Creation of a New Macrolide Antibiotic against Non-tuberculous *Mycobacterium* by Late-stage Boron-mediated Aglycon Delivery

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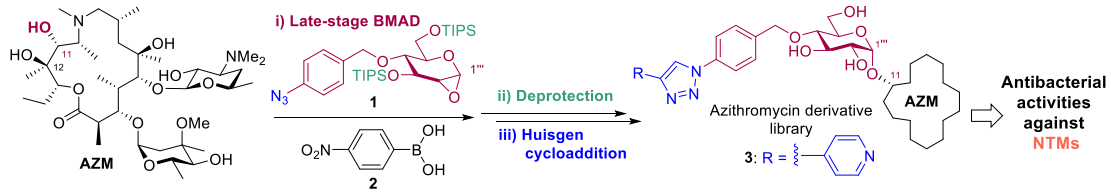
Non-tuberculous mycobacteria (NTM) is a recently emerging pathogen causing the pulmonary NTM disease. The macrolide azithromycin (AZM) is the standard first-line antibiotic for the treatment of the disease. However, the rise of drug-resistant NTM necessitates the development of novel therapeutics. In this context, our laboratory has developed the late-stage boron-mediated aglycon delivery (BMAD), which can efficiently introduce a sugar moiety regio- and 1,2-*cis*-stereoselectively to unprotected glycosides under mild conditions.[1)] Herein, we report on the development of a late-stage modification method of AZM utilizing BMAD, and its application to the creation of a new lead compound with higher antibacterial activity not only against wild-type NTM but also against macrolide-resistant NTM.

Initially, we designed a new library of AZM derivatives that were expected to express high binding activity to the 23S rRNA of macrolide-resistant NTM, by introducing various functional groups via glucose at position C-11 of AZM. Next, BMAD reaction of AZM and **1** using a catalytic amount of boronic acid **2** was examined. It was found that the glycosylation proceeded regio- and stereoselectively, and the subsequent deprotection of the silyl groups and Huisgen cycloadditions with various acetylene compounds provided a library of AZM derivatives in good yields. Next, the antibacterial activities of the library against NTMs (*M. avium* and *M. intracellulare*) were evaluated by broth dilution method. As a result, it was found that AZM derivative **3** exhibited effective antimicrobial activity against not only wild-type NTM but also macrolide-resistant NTM, thus successfully creating a promising new lead compound against pulmonary NTM disease.[2)]



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